

# Introduction to Molecular Modeling and Computer Simulation

S. *Ravichandran*, Ph.D.

Advanced Biomedical Computing Center  
Bldg. 430, NCI-Frederick, Frederick, MD 21702

E-mail: [sravi@ncifcrf.gov](mailto:sravi@ncifcrf.gov)

Tel: X1991

Web: <http://nciiris.ncifcrf.gov/~ravichas/MM/MM.htm>

<http://ncisgi.ncifcrf.gov/~ravichas/MM/MM.htm>

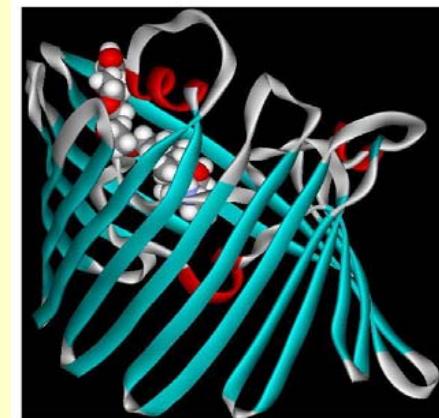
# Advanced Biomedical Computing Center

- Web:  
<http://www.abcc.ncifcrf.gov>
- Scientific Applications Page
- New Account
- Contacting the Help Desk

The screenshot shows the homepage of the Advanced Biomedical Computing Center (ABCC). The header features the ABCC logo and the text "ADVANCED BIOMEDICAL COMPUTING CENTER" and "A Center Devoted To Biocomputing". Below the header is a navigation bar with links for Home, Jobs, Search, Sitemap, About ABCC, Science, Resources, Communications, Training, Links, and Contact Us. A DNA helix graphic is positioned between the navigation bar and the main content area. The main content area includes a "SPOTLIGHT" section announcing that NCI was awarded the Grand Prize in Bio-IT World, featuring two trophy images. Below this is a news article about the award. To the right of the spotlight are several sidebar boxes: "Latest News" (with links to Renewal Surveys, Applications Form, GeneGo's MetaCore™, and News Archive), "NCI Licensed Scientific Softwares" (with links to ABCC Licensed Softwares and NCI ISCS -- Bethesda), "Training | Seminars News" (with links to Pharmacophore Modeling & Database Searching using Catalyst, Agilent Technologies: GeneSpring DNA Microarray Informatics Training Seminar, and Training | Seminars News Archive), "Molecular Modeling News" (with links to Download NCI Diversity AutoDock File, ABCC Obtained License For Accelrys Software Packages, List of Accelrys Software, and Molecular Modeling News Archive), and "Applications | Databases" (with links to Database List, External Links, Desktop Applications, List Of Applications, Bioinformatics OR Quantum Chemistry, Molecular Modeling OR Molecular Visualization, XRay/NMR Structure Refinement, Other Scientific Applications, Seqweb, Sequence Analysis using GCG Wisconsin Package, and GRID Database). The "List Of Applications" link in the "Applications | Databases" sidebar is circled in red, and an arrow points from it to the "Contact Us" link in the top right corner of the page.

# Overview of the class

- What is Molecular Modeling?
  - Basic assumptions etc.
- Where do we get these models?
  - Model Building, Databases
- Displaying models and model properties?
  - Graphics
  - Properties: Hydrophobicity, electrostatics etc.
- Simulating the models
  - Techniques: MM, MD, QM
- Selected Applications
  - Protein-ligand docking, Pharmacophore Modeling
- Hands on exercise: DSViewerPro 6.0
  - Small Molecule building, Energy Minimization
  - Aligning small molecules
  - Protein structure visualization



Porin

*Using DSViewerPro*

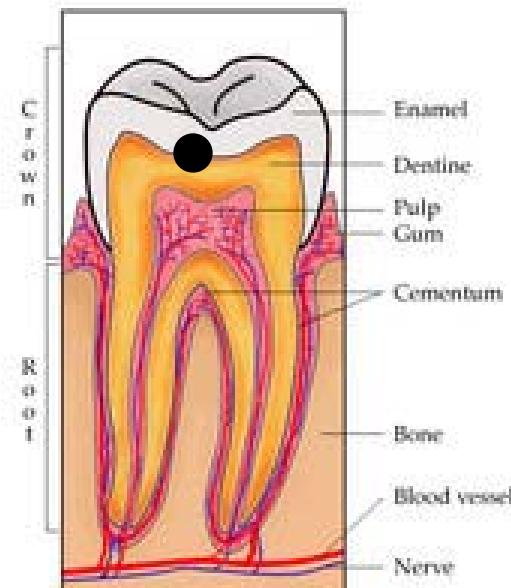
# Models

- Models are central to the understanding of the concepts in Chemistry/Biology
- Models are the result of mathematical equations
  - Classical and Quantum Mechanical
- Models have to be build carefully
  - Experimental information has to be taken into effect during model building

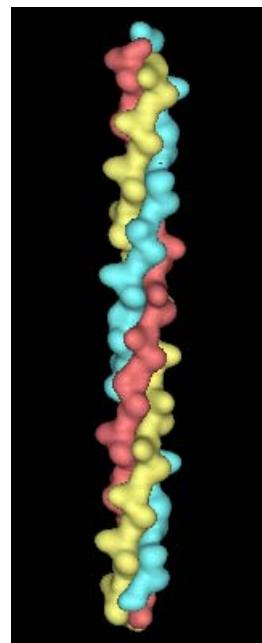
## Definition

Molecular Modeling is the science of creating model structures (numerically) and simulating its function using Classical or Quantum Mechanical laws

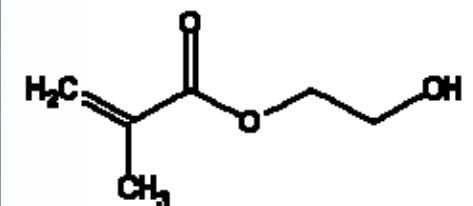
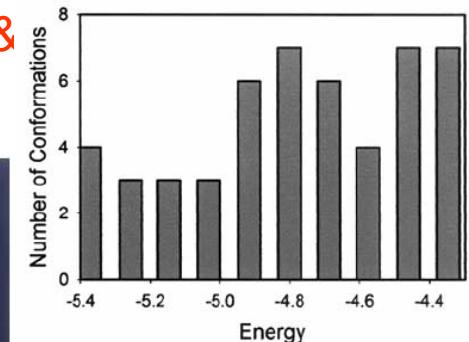
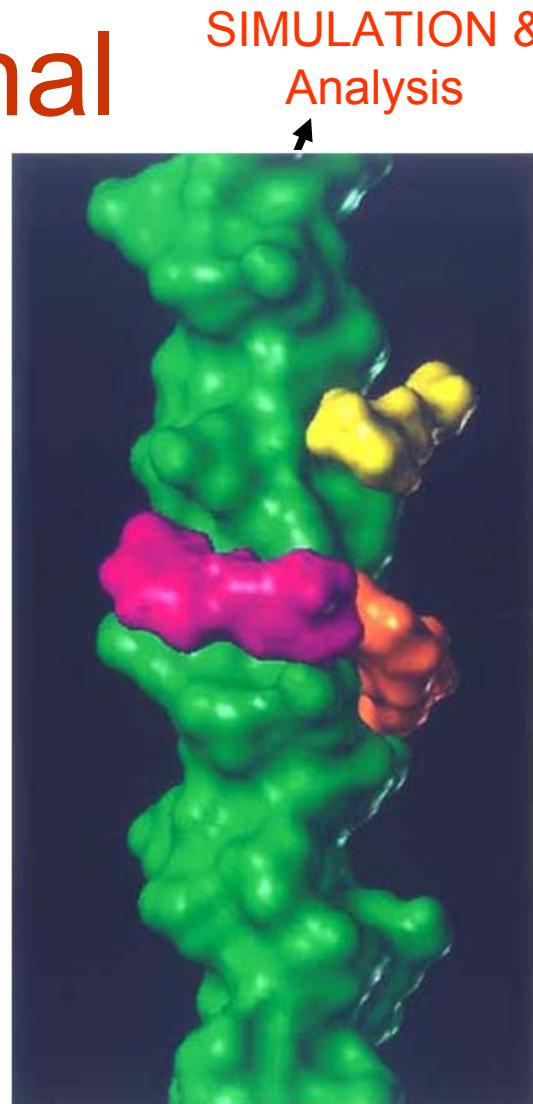
# Modeling Dentinal Adhesion



Tooth Image Wikipedia



SYSTEM  $\xrightarrow[\text{Approximation}]{\text{Simplify}}$  MODEL



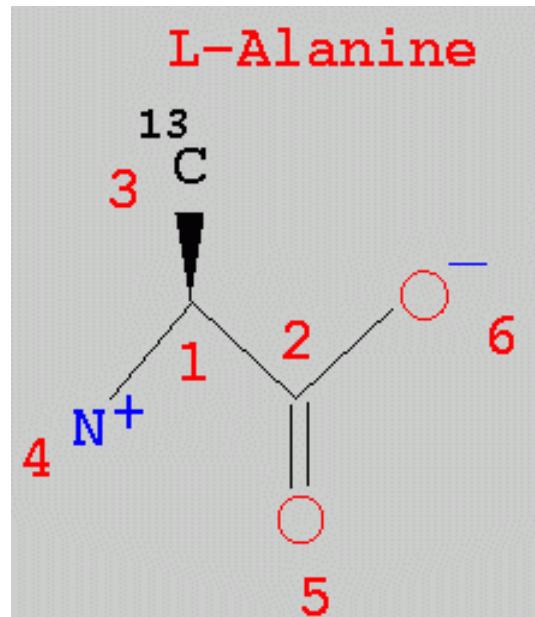
HEMA with Collagen

- Binding-Prof. T.K. Vaidyanathan and Jaya Vaidyanathan  
NJ Dental School, UMDNJ

# Getting Small Molecules

- Databases
  - Cambridge Structural Database (Experimental)
- Sketching
  - User sketches the molecule on the computer and the software converts into a proper 3D molecule (bond-angle, bond length etc.)
    - Sybyl, InsightII.....
- Fragment Libraries
  - Fragments are available in the software library. User builds the molecule using the fragments as a LEGO blocks
    - Sybyl, InsightII,.....
- 2D-3D conversion tools
  - Omega, CORINA, CONCORD etc.
    - ABCC has license for Omega

# MDL 2D file format (CTFILE)



Exercise 1: 2D SD File

6 5 0 0 1 0	3 V2000	Counts Line
-0.6622 0.5342	0.000 C 0 0 2 0 0 0	
0.6622 -0.3000	0.000 C 0 0 0 0 0 0	
-0.7207 2.0817	0.000 C 1 0 0 0 0 0	Atom
-1.8622 -0.3695	0.000 N 0 3 0 0 0 0	Block
0.6220 -1.8037	0.000 O 0 0 0 0 0 0	
1.9464 0.4244	0.000 O 5 0 0 0 0 0	
1 2 1 0 0 0		
1 3 1 1 0 0		
1 4 1 0 0 0	Bond Block	
2 5 2 0 0 0		
2 6 1 0 0 0		
M CHG 2 4 1 6 -1	Properties Block	
M ISO 1 3 13		
M END		

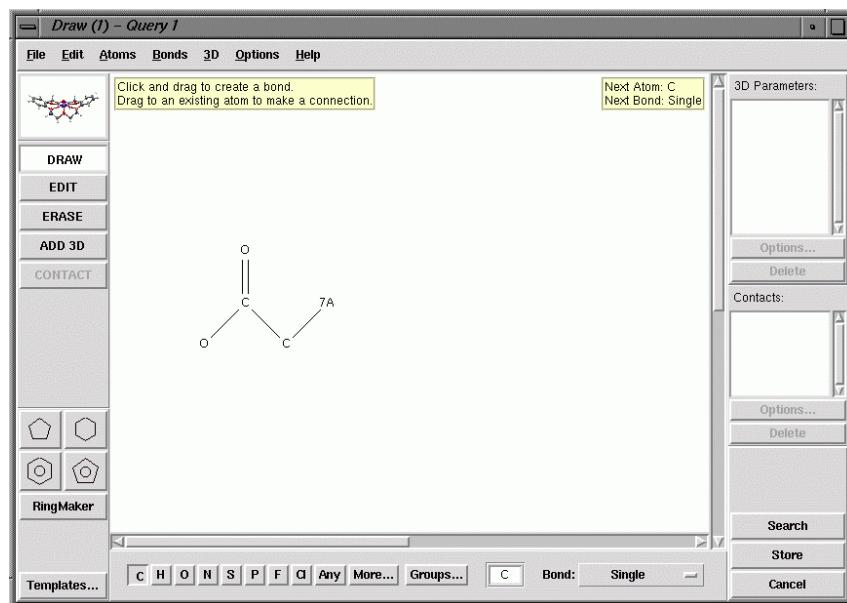
Connection  
Table (Ctab)

# Cambridge Structural Database (CSD)

- X-ray and neutron diffraction analysis of carbon-containing molecules (up to 1000 atoms including H)
  - Organics, Organometallics, Metal Complexes
  - Peptides up to 24 residues
  - mono-, di- and tri-nucleotides
- Different Search Options:
  - Basic substructure, Substructure with constraints, 3D substructure, non-bonded interactions, Pharmacophore, Cell parameter, Journal Reference

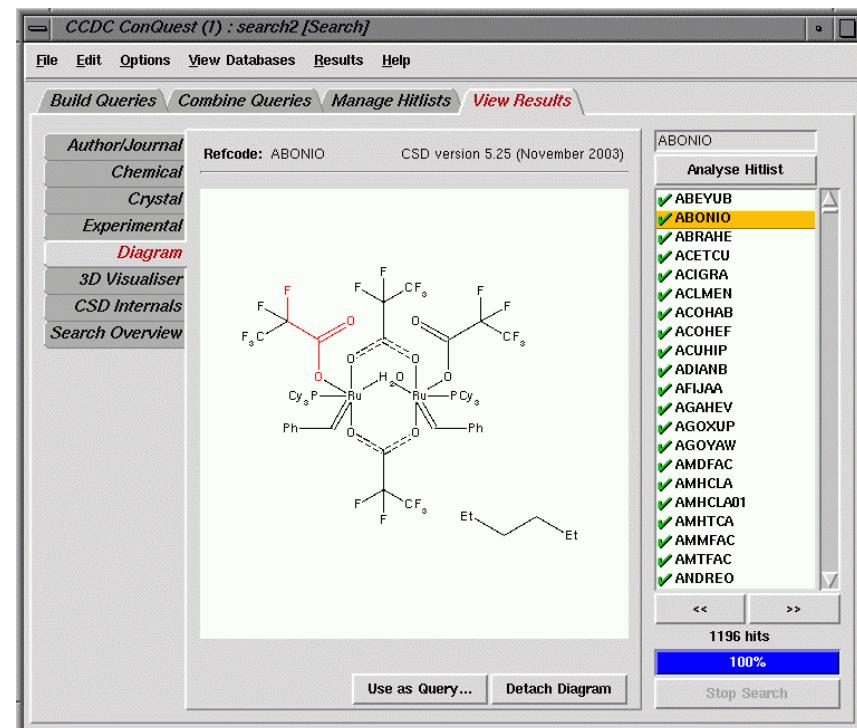
# CSD: Substructure Search

Query



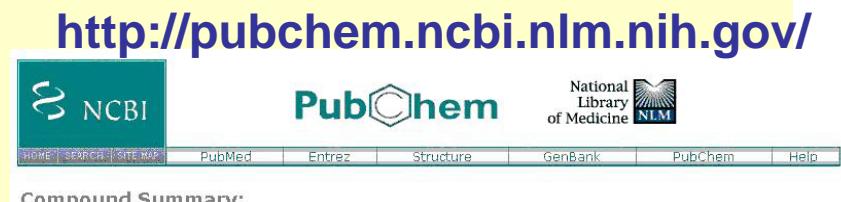
7a : any halogen

Result



# Pubchem database (NIH)

- Pubchem: Library of small molecules
  - Structures, activities
  - How to search?
    - Compound search
      - using names, synonyms, keywords, identifiers
    - Substance search for deposited structures
      - using names, synonyms, keywords, identifiers
    - Bioassay search for description
      - using names (ex HIV growth inhibition)
    - Structure search
      - using example SMILES, mol files



# 3D-Structural Database of biomolecules (PDB)

<http://www.rcsb.org>

PDB: 50  
structures  
(1975)

- NMR (early 1960s)
  - Dynamic
    - Multiple Models (Each conformation is a model)
  - Aqueous environment
  - Limitations
    - Size of molecule
      - < 30kD
- Examples
  - 1DV0, 1UBA

NMR: 3776  
X-ray: 24334  
Total: 28110

May 10, 2005

03/14/2007

NMR: 6132  
X-ray: 35722  
e- micros: 143  
Total: 42082

Mar 06, 2007

- X-ray (1958)
  - Static
    - Only one model
  - Crystal
  - Limitations
    - Not limited by size
- Examples
  - 7LYZ, 2SRC

NMR: 5409  
X-ray: 31223  
e- micros: 125  
Total: 36837

Jun 01, 2006

S. Ravi chandran, ABCC,  
NCI -Frederick

# Anatomy of PDB file

Atom #

Residue

Residue #

Chain ID

X Y Z Occ

Temp Factor

Only portion of the file is shown

ATOM	1	N	MET	B	1		52.127	-7.410	40.963	1.00	52.97
ATOM	2	CA	MET	B	1		51.096	-6.600	40.340	1.00	52.20
ATOM	3	C	MET	B	1		51.305	-6.416	38.831	1.00	51.74
ATOM	4	O	MET	B	1		52.405	-6.086	38.379	1.00	50.94
ATOM	5	CB	MET	B	1		51.012	-5.245	41.044	1.00	52.27
ATOM	6	CG	MET	B	1		50.777	-5.353	42.542	1.00	50.84
ATOM	7	SD	MET	B	1		49.355	-6.390	42.934	1.00	51.51
ATOM	8	CE	MET	B	1		48.078	-5.169	43.363	1.00	47.75
ATOM	9	OXT	MET	B	1		50.932	-9.312	40.816	1.00	53.41
ATOM	11	N	ASN	B	2		50.235	-6.630	38.064	1.00	50.80
ATOM	12	CA	ASN	B	2		50.271	-6.496	36.613	1.00	49.26
ATOM	13	C	ASN	B	2		50.332	-5.038	36.246	1.00	48.37
ATOM	14	O	ASN	B	2		50.120	-4.673	35.089	1.00	50.24
ATOM	15	CB	ASN	B	2		49.016	-7.074	35.977	1.00	49.62
ATOM	16	CG	ASN	B	2		48.753	-8.479	36.395	1.00	51.39
ATOM	17	OD1	ASN	B	2		49.628	-9.339	36.316	1.00	51.26
ATOM	18	ND2	ASN	B	2		47.531	-8.701	36.861	1.00	54.69
.....	.....	.....	.....	.....	.....		.....	.....	.....	.....	.....
HETATM	2462	ZN	ZN		909		45.731	9.445	45.851	0.54	77.21
HETATM	2463	C1	RET	B	978		33.234	8.591	25.798	1.00	34.05
HETATM	2464	C2	RET	B	978		31.995	8.387	24.968	1.00	33.95
HETATM	2465	C3	RET	B	978		32.242	8.645	23.513	1.00	33.45
HETATM	2466	C4	RET	B	978		32.720	10.104	23.258	1.00	33.69
HETATM	2467	C5	RET	B	978		33.717	10.591	24.302	1.00	34.43
HETATM	2468	C6	RET	B	978		33.938	9.900	25.443	1.00	34.95
HETATM	2469	C7	RET	B	978		34.915	10.362	26.451	1.00	36.11

# More about PDB Structures

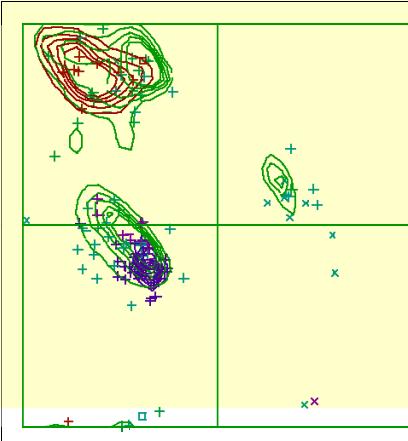
- These crystallographic databases gives information w.r.t a crystal environment
  - Proteins NMR studies have shown that the structure in the crystal phase and solution phase are almost same but for small molecules this may not be the case
  - These databases do not cover the whole spectrum because some of the molecules cannot be crystallized

# No Experimental Macromolecule Structure & Homology Modeling

- No 3D structure but has homologous PDB entries
  - Can exploit homology to model the unknown protein
    - Accelrys (Modeller), Swiss-Model, Tripos (Matchmaker )
- No 3D structure but do not have any homologous PDB entries
  - Threading, Reverse Folding
    - Tripos (GenFold)

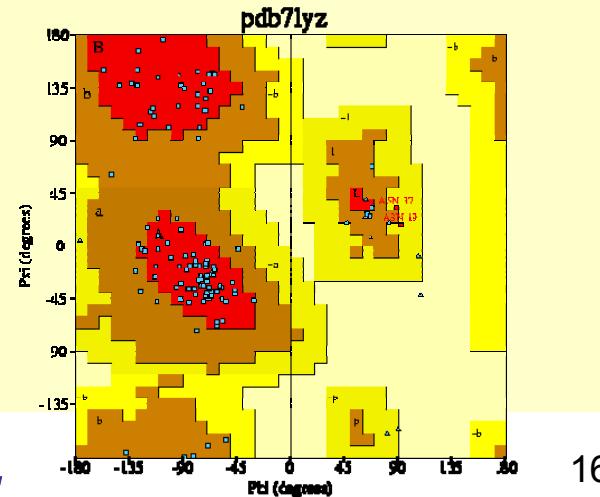
# Quality (model) check!

- Procheck: Stereo-chemical quality of the protein and residue by residue analysis in figures  
<http://www.biochem.ucl.ac.uk/~roman/procheck/procheck.html>
- PDBREPORT: <http://www.cmbi.kun.nl/gv/pdbreport>



03/14/2007

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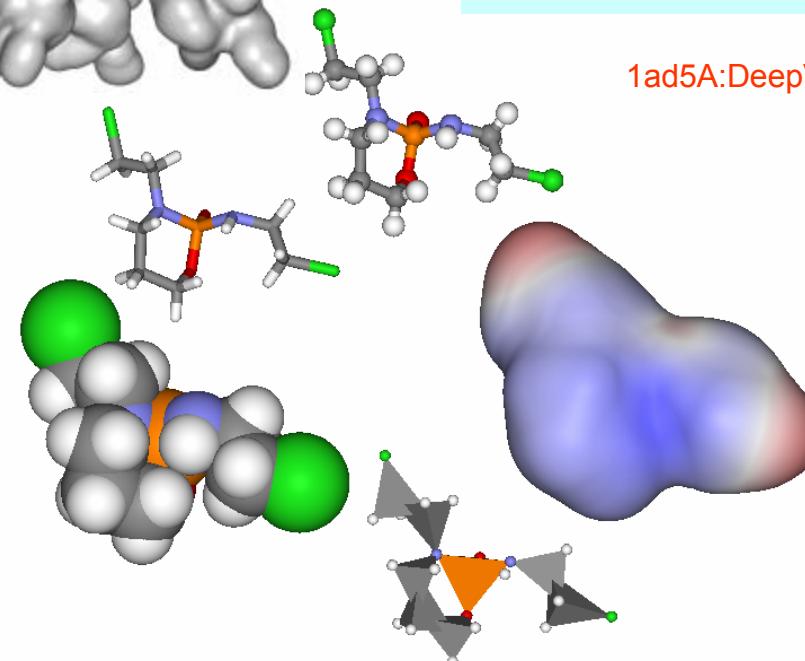
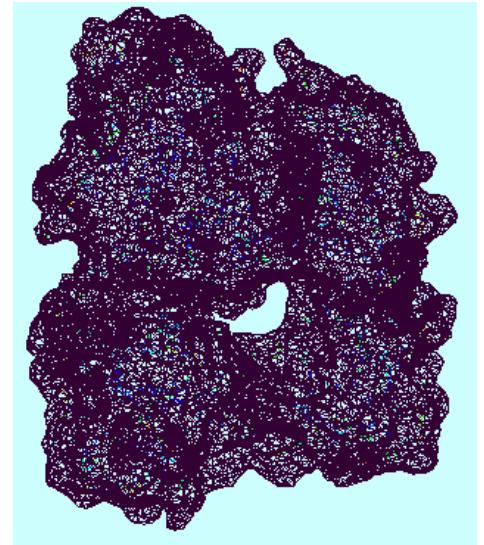
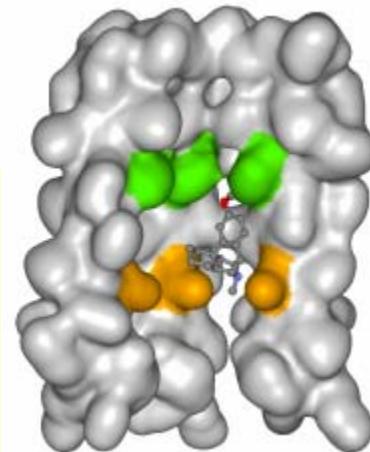


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# Molecular Modeling: Visualization

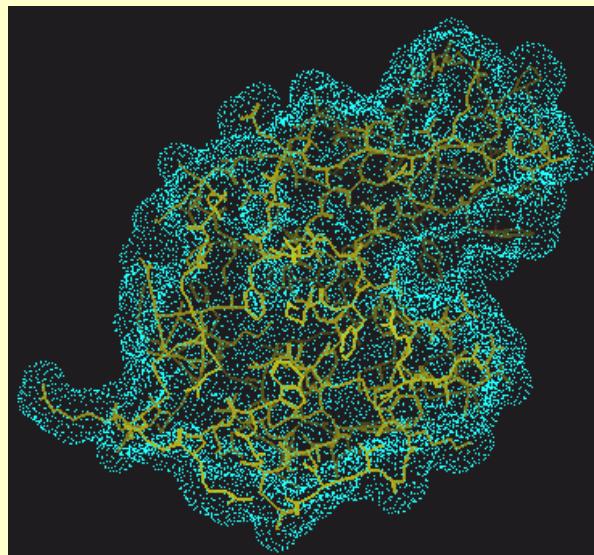
- Visualization
  - Free: [Spdbv](#), [Cn3D](#), [Rasmol](#), [VMD](#) and many more
  - \$\$\$: Tripos, [Accelrys](#) and many more

Discovery Studio 1.6-a3b2 Receptor



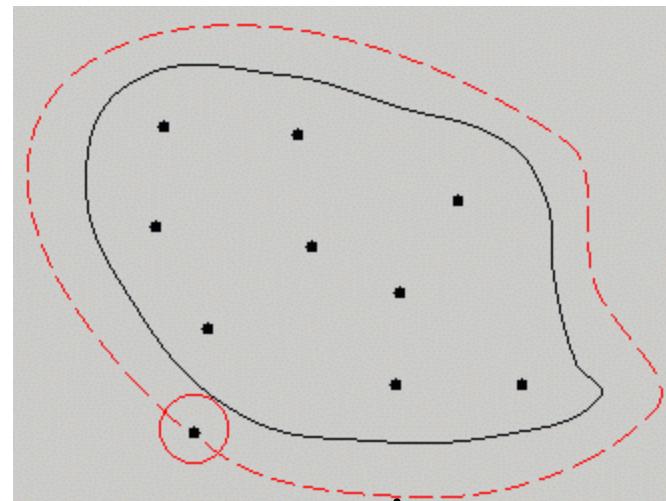
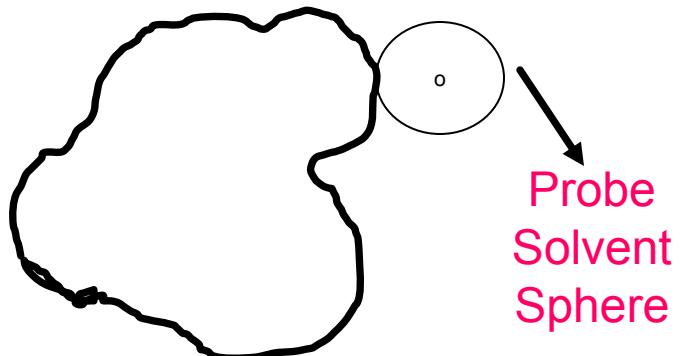
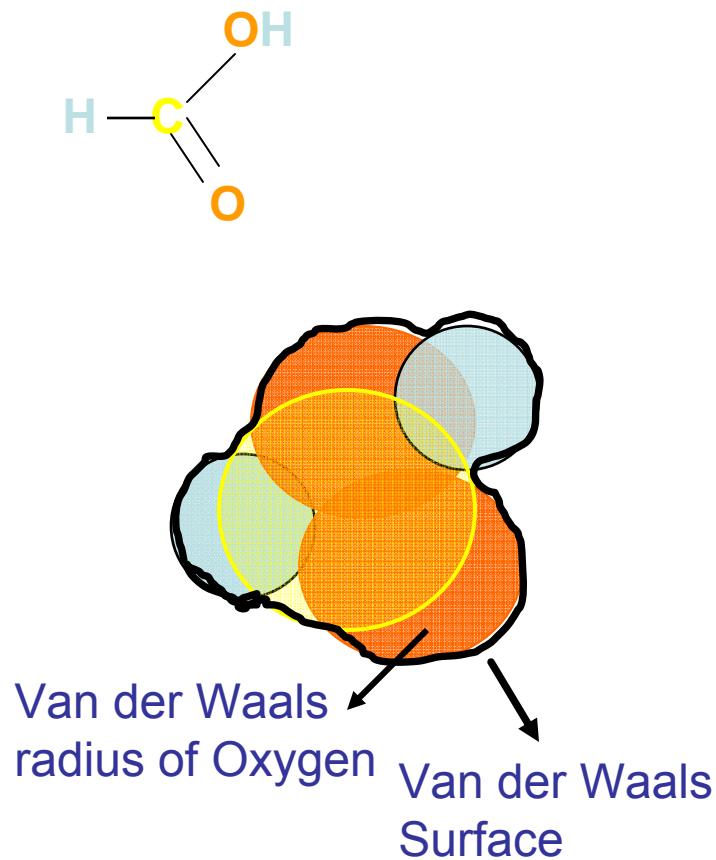
R-Ifosfamide Discovery Studio ViewerPro 6.0

# Selected Static properties of Maromolecules: SA

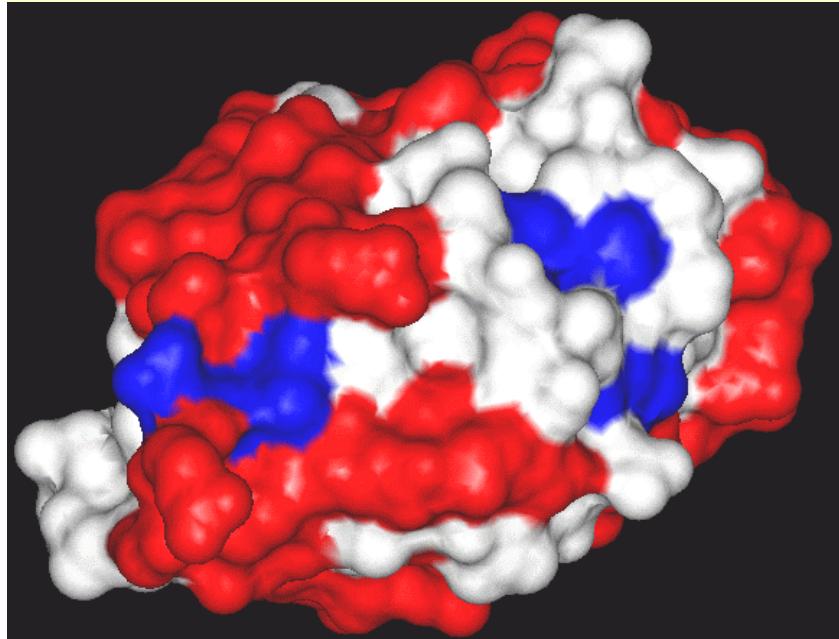


- Solvent-Accessibility (SA)
  - SA help us to know what groups are on the surface-solvent exposed
    - Can give hints on the possible interaction with ligands etc.

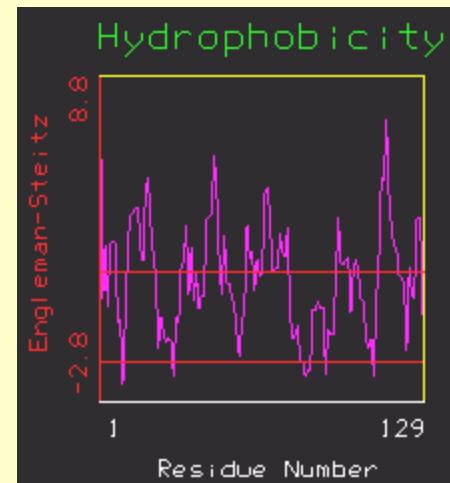
# Molecular Surfaces



# Molecular Surface

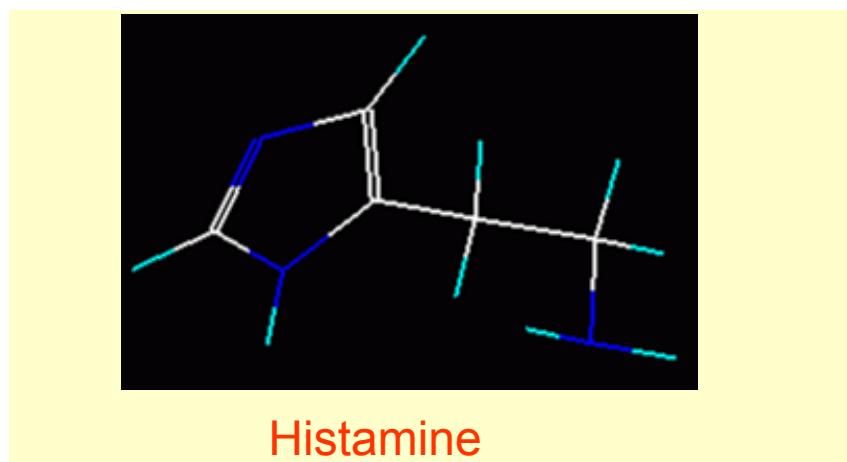
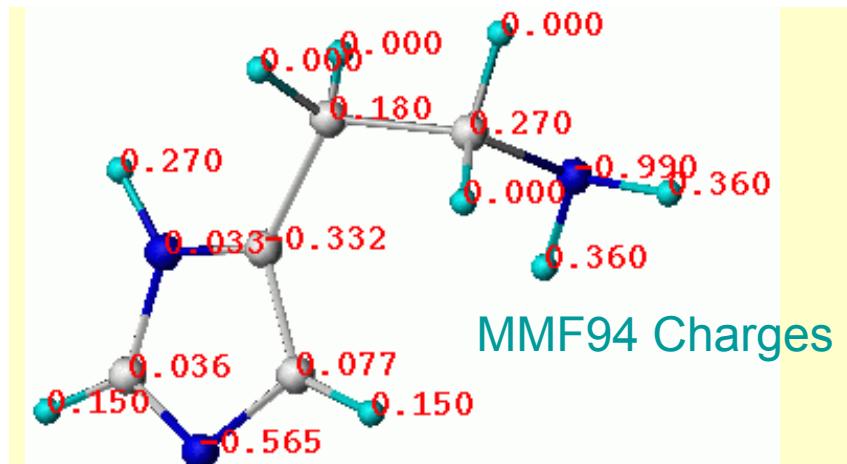


Hydrophobic residues on  
the Connolly surface of the  
protein for some reason!  
Protein-Protein Interactions



Lysozyme, Hydrophilic red, hydrophobic blue, InsightII,  
subsets are created using Engleman-Steitz algorithm

# Partial Charges



- Classical View
  - Valence electrons fixed to atoms
- Modern View:
  - Diffused
  - Electrons spend more time near electronegative atoms
    - Charges on Nitrogen are different (positive and negative)

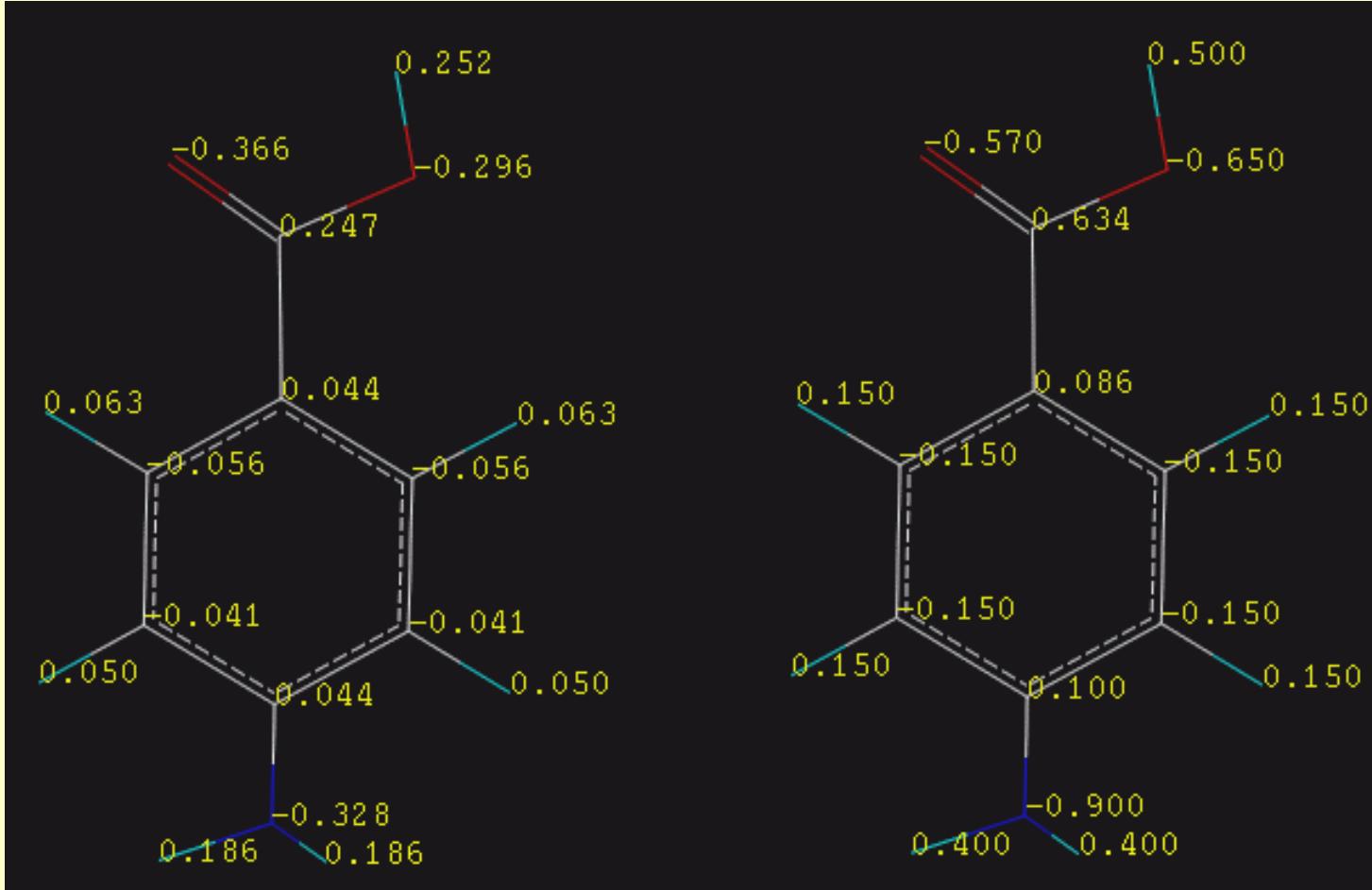
# Point charges

- Quantum method:

Electrostatic Potential  
**(ESP)** Fit method:  
Recent and  
promising method

1.  $\psi$  (*ab initio*/semi-empirical)
2. Charge Density from  $\psi$
3. Mulliken Population Analysis  
takes the charge density and partitions between atoms based on occupancy of each orbital

# Partial Charges



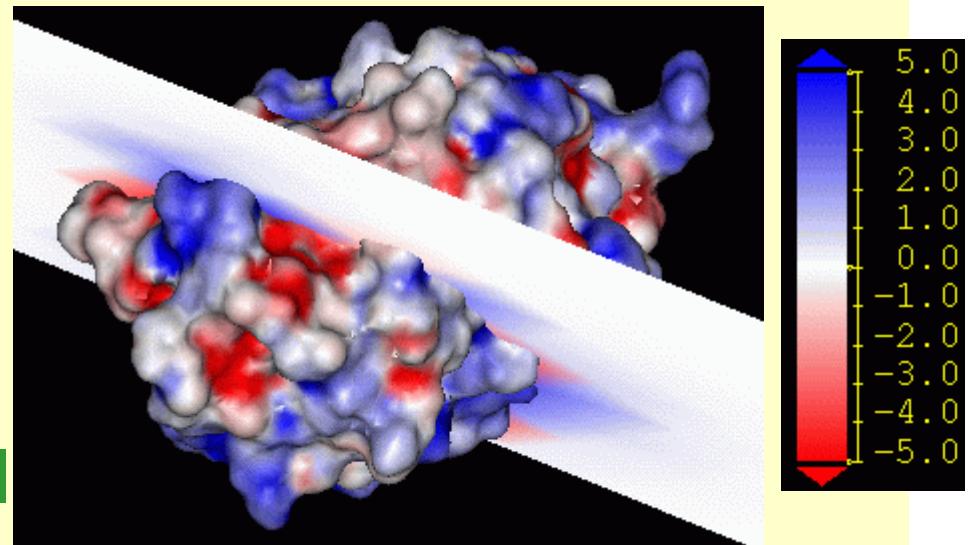
Gasteiger-Hückel

MMF94

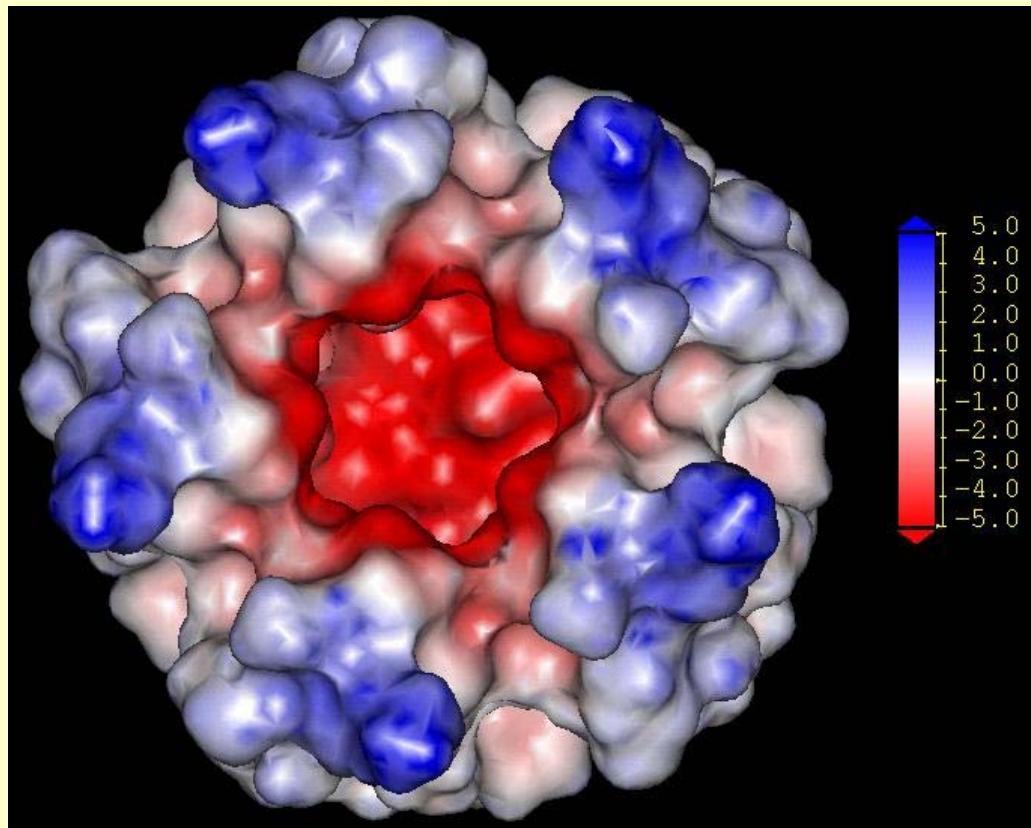
# Electrostatics

- Delphi: software to calculate electrostatic properties-Protein-Ligand interactions
  - Calculate electrostatic potential
  - Effects of site-directed mutagenesis
  - Electrostatic contribution to the solvation energy
  - Interface to InsightII

Picture made with InsightII



# Electrostatics

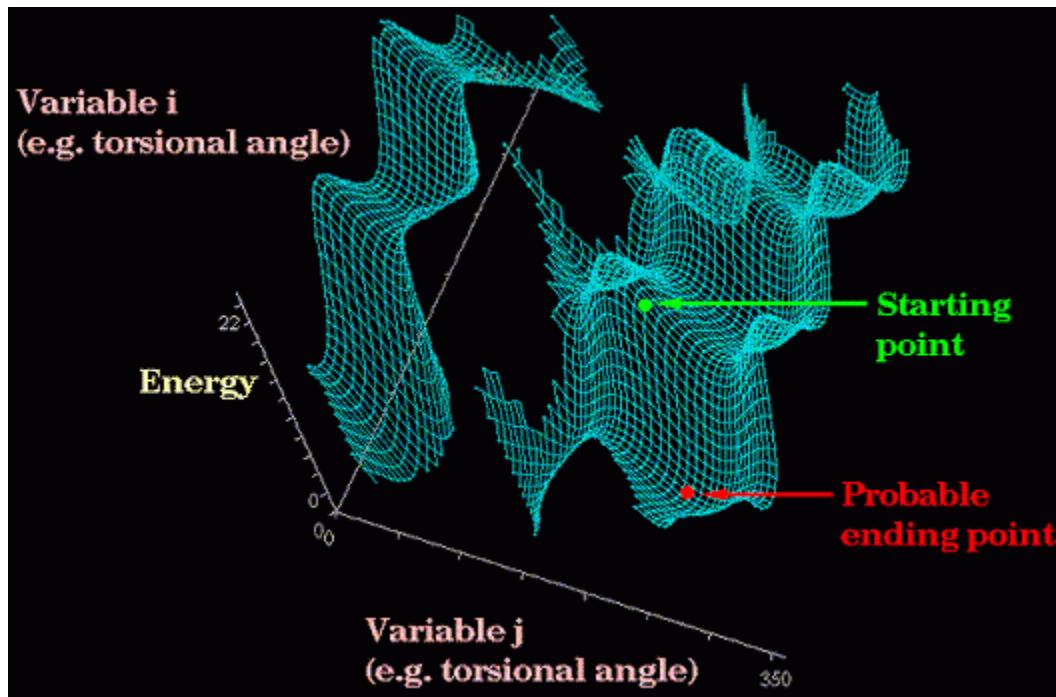


# Computer Simulation

# Molecular Mechanics (MM)

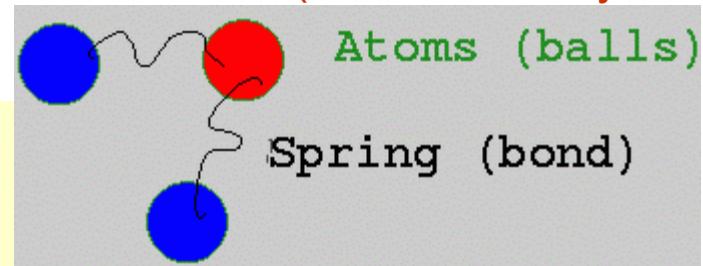
- What is Molecular Mechanics?
  - MM is a energy refinement procedure. Refinement process Is usually called Minimization or Energy Minimization.
  - Assumption: Energy minimized structure is closer to the stable geometry and probably closer to experimental structure.
- Where Energy Minimization is usually employed?
  - Molecule Building, Homology modeling, Conformational Search, PDB file refinement

# MM



NIH Molecular Modeling

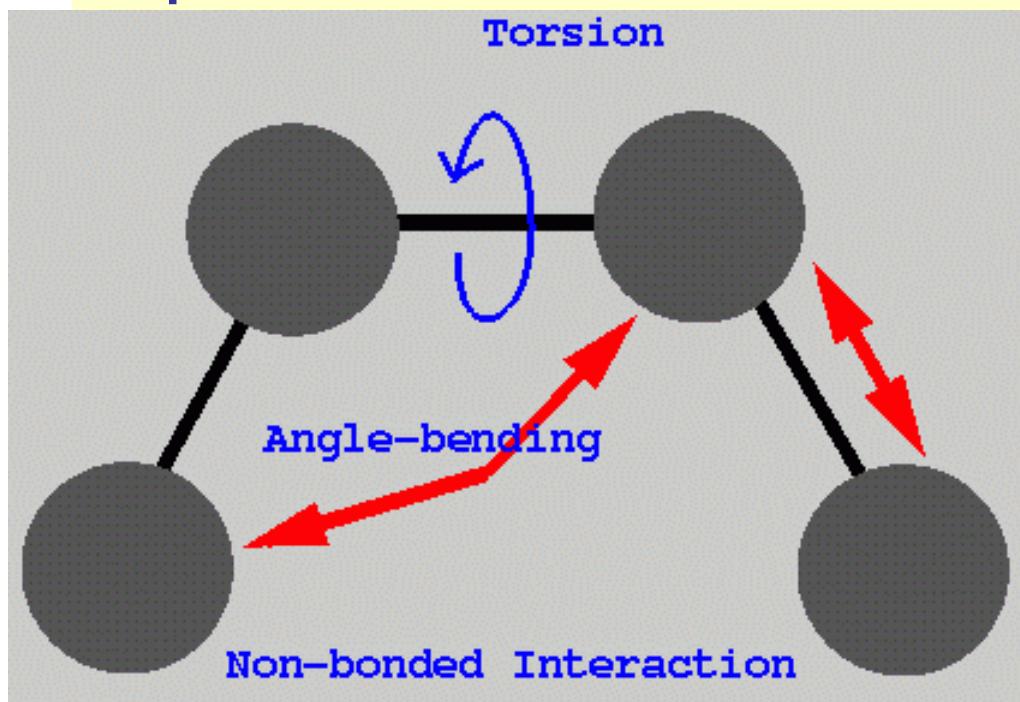
# Basic assumptions of MM<sub>(1960's to early 70s)</sub>



- Electrons and nuclei are lumped together
  - Born-Oppenheimer Approximation
    - Separation of electron ( $e^-$ ) movement (fast) from the slow nuclei (X)
      - $E(X, e^-) \rightarrow E(X);$
      - where, X = Collective position vectors of the nuclei
  - Molecules are assumed to be soft balls (point masses) and connected to others by bonds (springs)
  - Total energy of the system is an important property and it is usually computed as a sum of independent energy terms.

# ForceField

- ForceField is an analytical Functional form for the independent energy terms and parameters



$$E_{\text{pot}} = \sum \frac{1}{2} K_b (b - b_0)^2 + \sum \frac{1}{2} K_\theta (\theta - \theta_0)^2 +$$

$$\sum \frac{1}{2} K_\phi (1 + \cos N\phi)^2 + \sum \frac{1}{2} K_\chi (\chi - \chi_0)^2$$


---


$$\sum ((B/r)^{12} - (A/r)^6) + \sum (q_1 q_2 / r)$$

↓                      ↓

VDW                    electrostatic

Bond Stretching =  $K(b-b_0)^2$   
Simple Functional Form

$$\text{Force} \rightarrow -\frac{\partial E}{\partial r_i}$$

- Additivity
  - Transferability of Force Field parameters

# MM



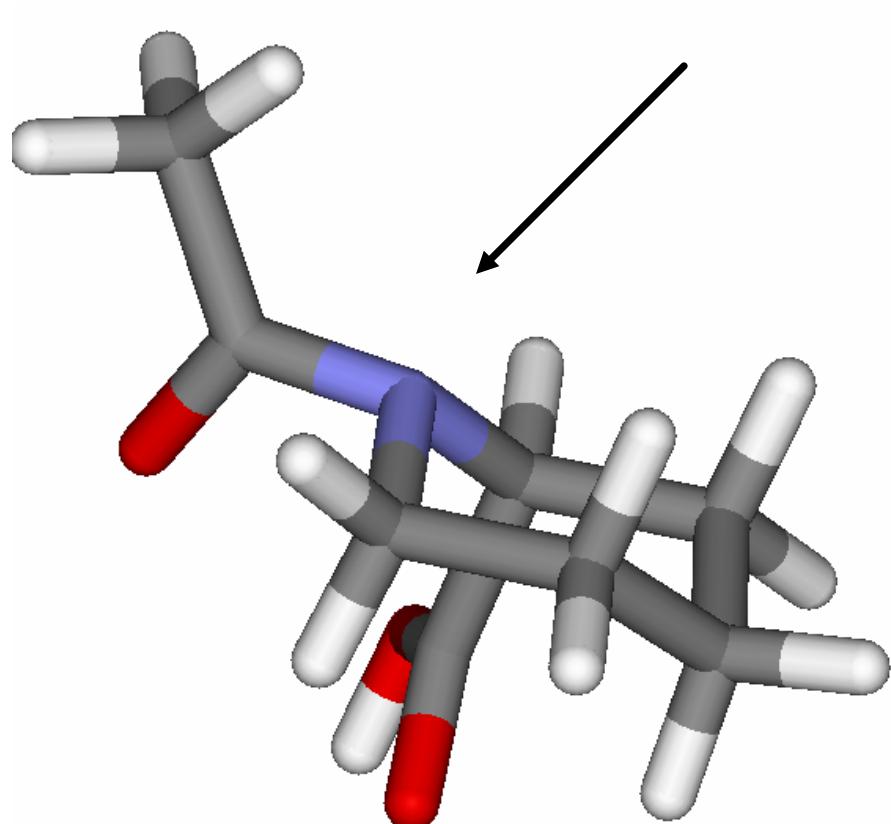
- Each atom/bond in a molecule or amino acid is identified by
  - 1) Atom type 2) Residue type 3) hybridization type 4) Bonding info. 5) Charges 6) Coordinates

## Carbon-di-oxide

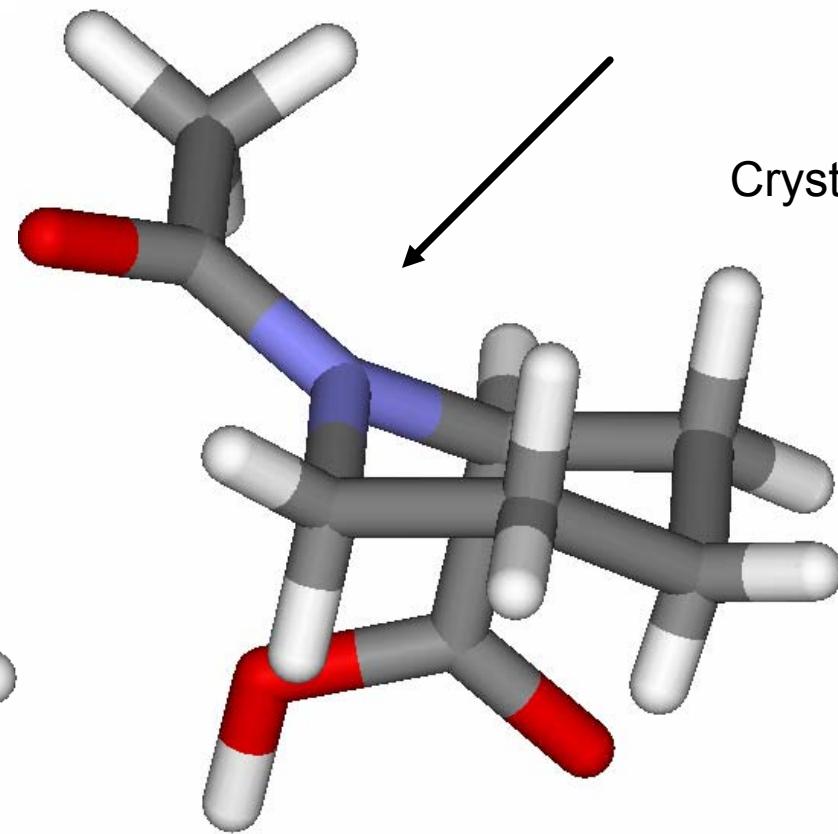
- Atom types C1, O2; Hybridization: sp, sp<sup>2</sup>; Bonding info: C1 is bonded to two O2 atoms; Coordinates: x,y and z; Charges: (C) 0.372, (O) -0.186

N-Acetyl-Piperidine-2-  
carboxylic acid

# AtomTypes/FF



N-Sp3



Experiments/QM Calclns

# Force Field (small molecules)

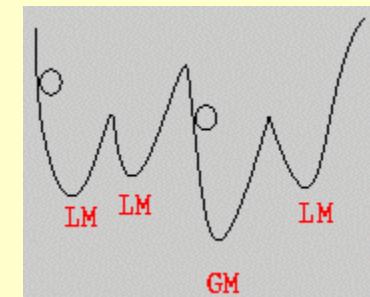
- Force Field for small molecules
  - Norman Allinger & co-workers (1977)  
<http://europa.chem.uga.edu/allinger/mm2mm3.html>
  - MM2 (1991)
    - Parameter update (1991), Functional update (1987)
  - MM3(2000) Latest Version of MM3
    - Extended to handle amides, polypeptides & proteins
  - MM4 (2003)
    - Emphasis on alkanes, non-conjugated alkenes, conjugated hydrocarbons and vibrational frequencies

# Force Field for biomolecules

- AMBER: Assisted Model Building with Energy Refinement (Peter Kollman at UCSF & Collaborators with groups from academics and industry)
  - Latest version (AMBER 8)
  - AMBER5 AMBER6: Cornell et al (1994) FF or parm94
- CHARMM
  - Chemistry at HARvard Molecular Mechanics (CHARMM) Martin Karplus (Cambridge MA)
    - <http://www.accelrys.com>
- GROMOS (GROningen MOlecular Simulation)
  - Wilfred Van Gunsteren & Herman Berendsen
    - Groningen (Netherlands)
- OPLS (Optimized Potential for Liquid Simulation)
- CVFF/CFF (Consistent Force Field)
- MMFF (Merck Molecular Force Field)
  - Thomas Halgren, Merck and Co.

# Energy Minimization

- Different Flavours of Energy Minimization:
  - Steepest Descent (SD)
    - SD is used to relieve overlaps and so good at start
  - Conjugate-Gradient (CD)
    - CD is slow but can lead to structures with low energies. Do not get trapped in local minima like SD!
  - Simulated Annealing



# MM

– Limitations: No guarantee that you will reach Global minimum

- Two alternative methods:  
MD or stepwise rotation of bonds

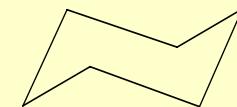
Example

Twist boat cyclohexane  
11.917 kcal/mol

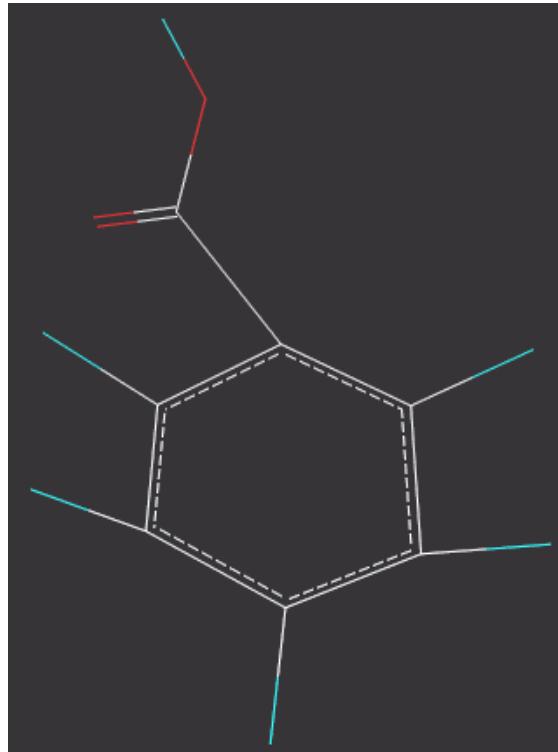
Molecular  
Dynamics

Chair form  
6.558 kcal/mol

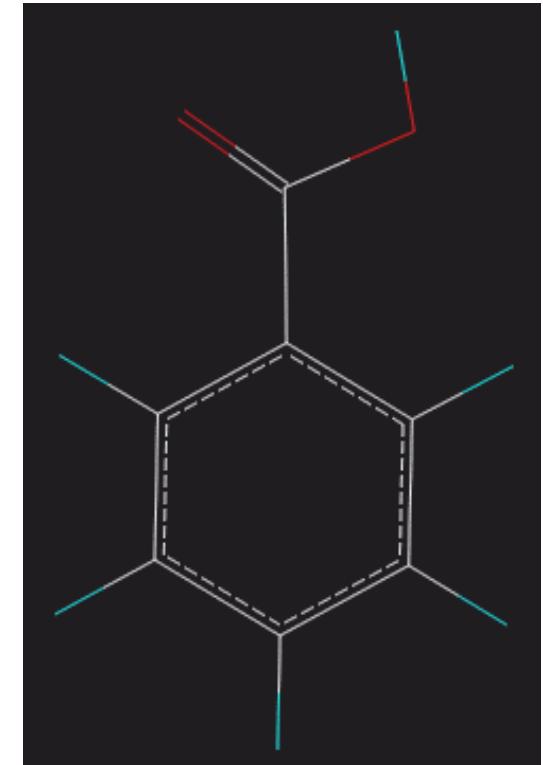
Cyclohexane  
remains in  
twist boat form  
in Molecular  
Mechanics



ACD/ChemSketch



Initial  
403.252  
kcals/mol



Final  
11.453  
kcals/mol

Bond Stretching Energy : 262.467  
Angle Bending Energy : 125.020  
Torsional Energy : 8.902  
Str-Bend Energy : 2.266  
Out of Plane Bending Energy : 0.242  
1-4 van der Waals Energy : 13.430  
van der Waals Energy : 2.285  
1-4 Electrostatic Energy : 8.111  
Electrostatic Energy : -19.471

Method:  
Powell

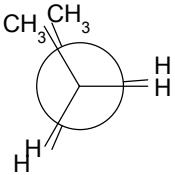
Termination:  
Gradient,  
0.05  
kcal/mol

Initial  
Optimization  
: Simplex

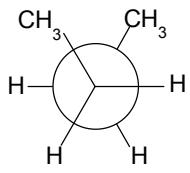
Bond Stretching Energy : 1.554  
Angle Bending Energy : 4.657  
Torsional Energy : 1.605  
Str-Bend Energy : 0.282  
Out of Plane Bending Energy : 0.000  
1-4 van der Waals Energy : 16.267  
van der Waals Energy : 0.506  
1-4 Electrostatic Energy : 5.516  
Electrostatic Energy : -18.934

# Conformational Analysis

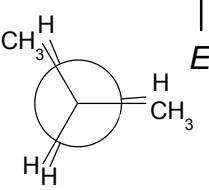
A Eclipsed



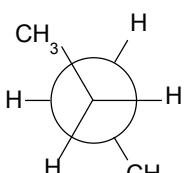
B Gauche



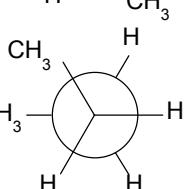
C Eclipsed



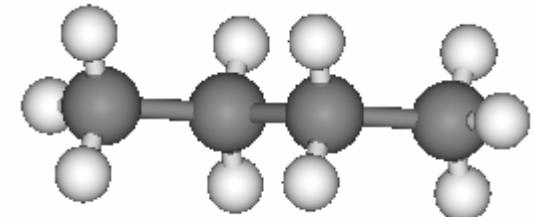
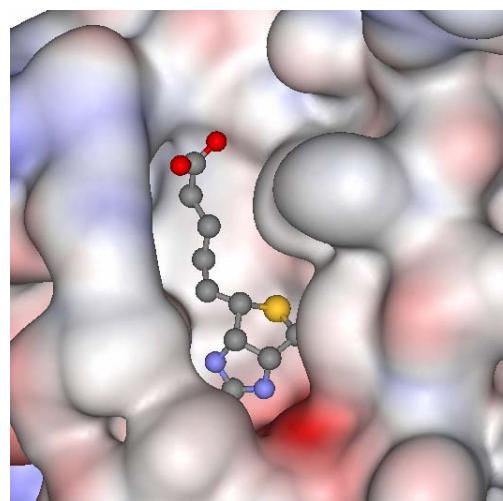
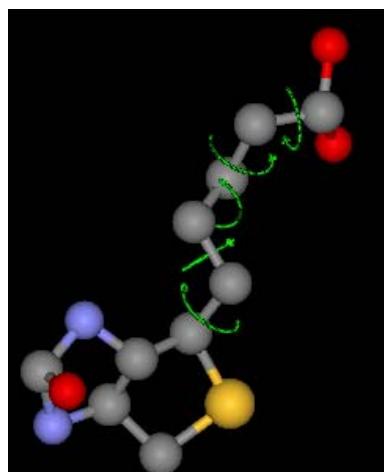
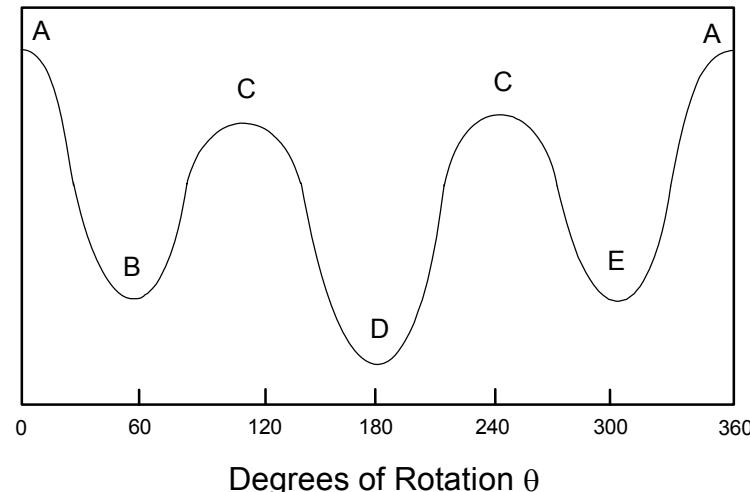
D Anti



E Gauche



Made using ACDLabs ChemSketch



Molecules are not rigid

They exist in conformers

For example  
70% anti-trans  
30% gauche form

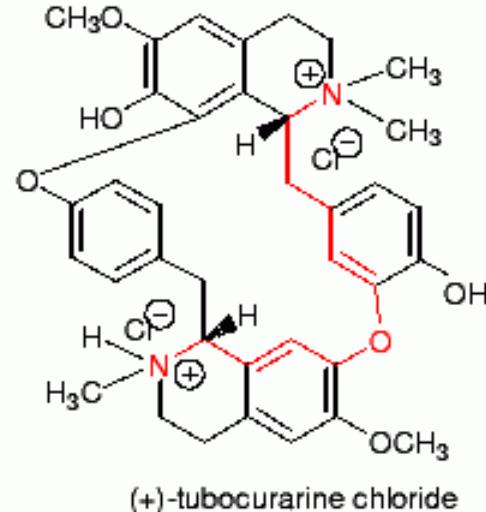
Biological activity of a drug molecule is supposed to depend on one unique conformation

1STP

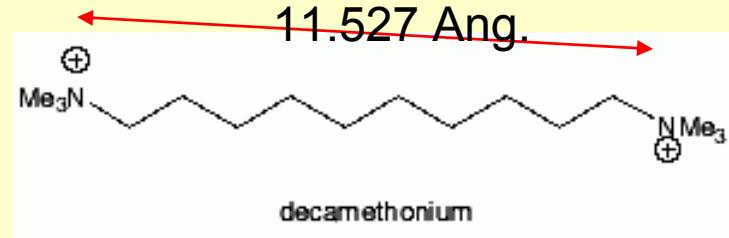
# Identifying Active Conformation?

- **X-ray structure**
  - Crystal structure of target protein with the ligand (drug)
    - Not all proteins can be crystallized (eg. membrane proteins)
- If active compound is a rigid molecule (not many conformations). Take the trial compounds and identify conformations that matches the template
  - MD to identify the conformation

Neuromuscular blocking agent-  
Pharmacopore: 2 Quaternary N atoms



(+)-tubocurarine chloride



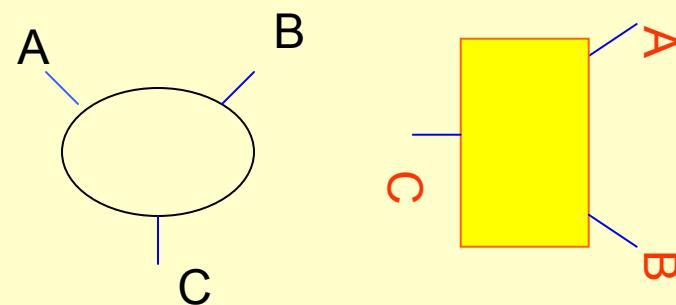
11.527 Ang.

decamethonium

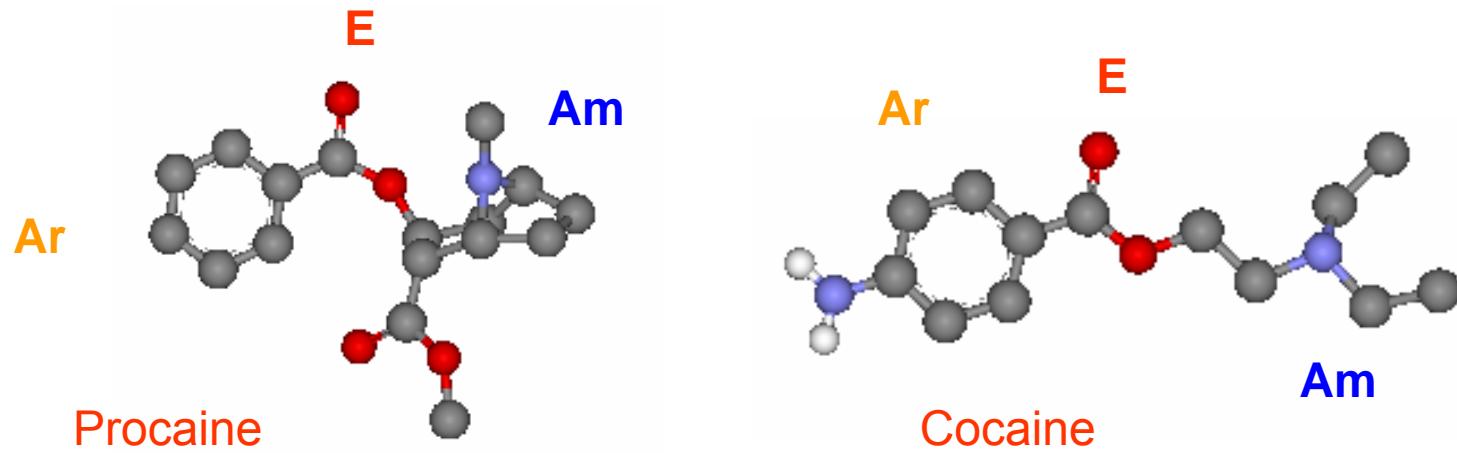
An Introduction to Medicinal Chemistry, Graham Patrick 2002

# Pharmacophore

- Pharmacophore: Group of atoms (functional group) common for active compounds w.r.t receptor and essential for its activity
  - Substructure
  - Chemical Functions



# Pharmacopore by Example



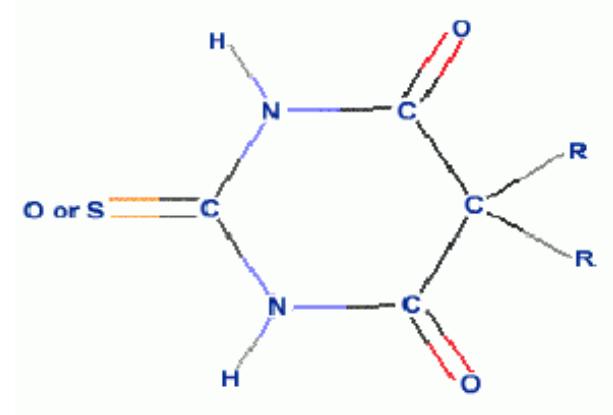
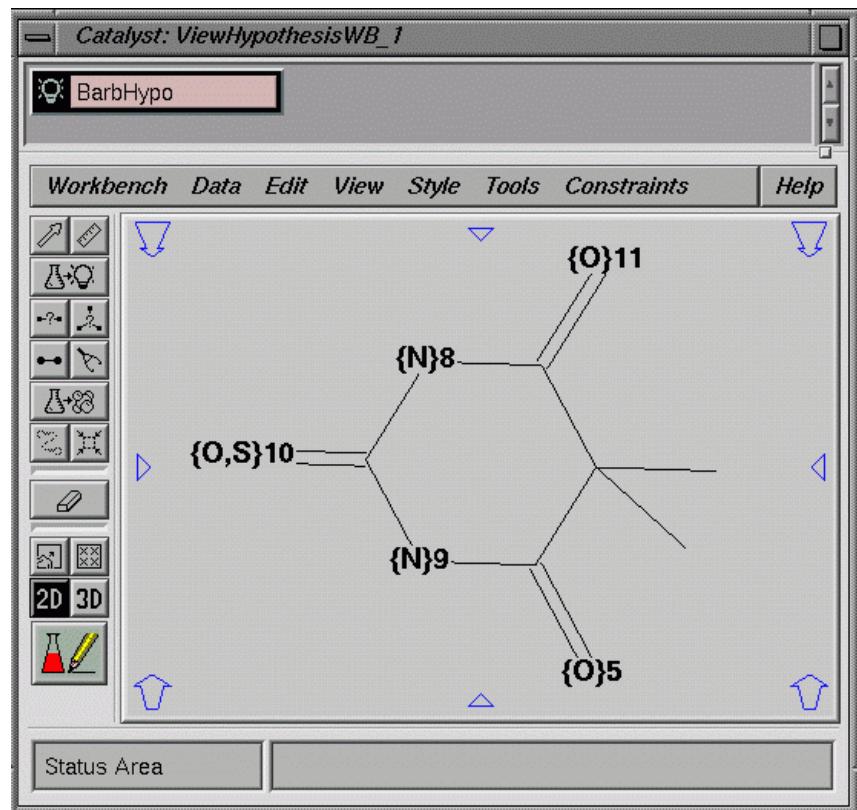
Both have anesthetic property.

QSAR studies indicate that the pharmacoporic (binding site) is related to the presence of **Ester(E)**, **Amine(Am)** and **Aromatic (Ar)** groups.

Pharmacopore here indicates not only the presence of same functional groups but also their presence in the same relative position

An Introduction to Medicinal Chemistry, Graham Patrick 2002

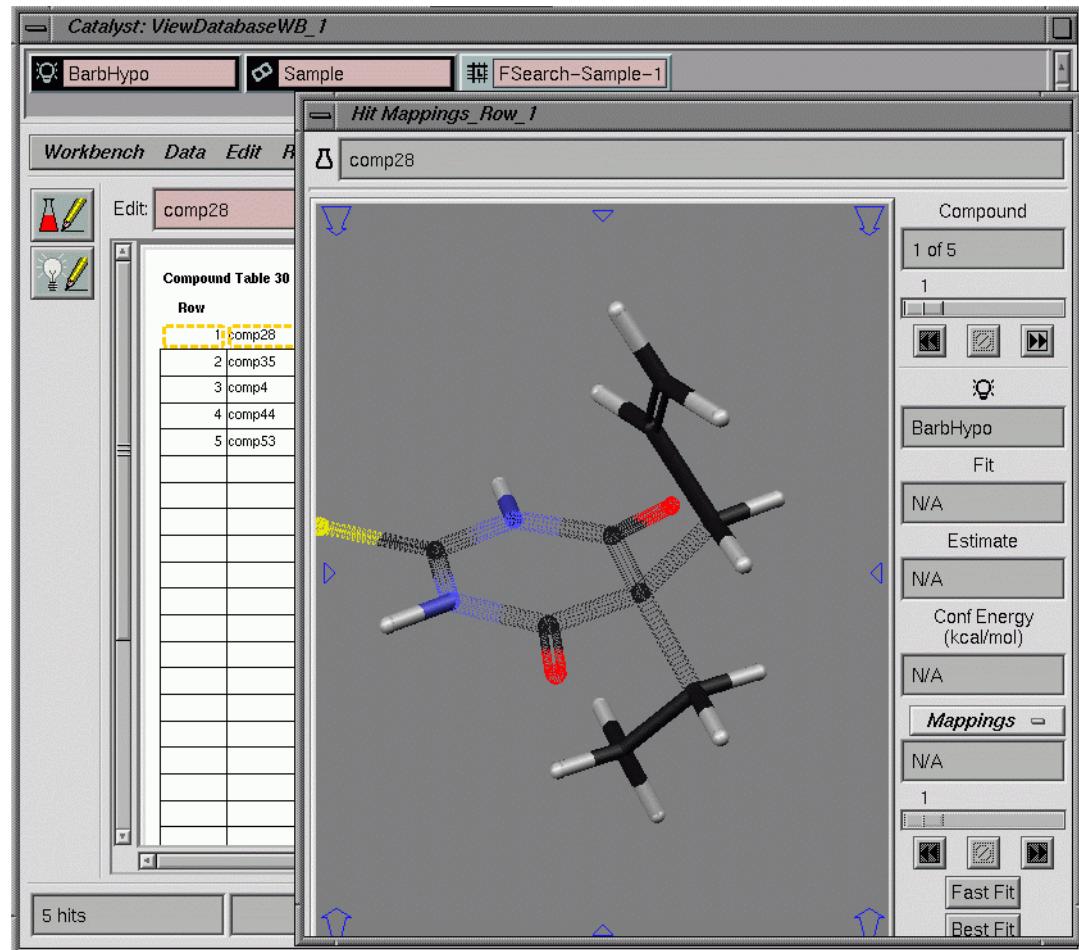
# Substructure Search



Substructure for generic barbiturate

Catalyst 4.9 Accelrys Inc.

# Substructure Search



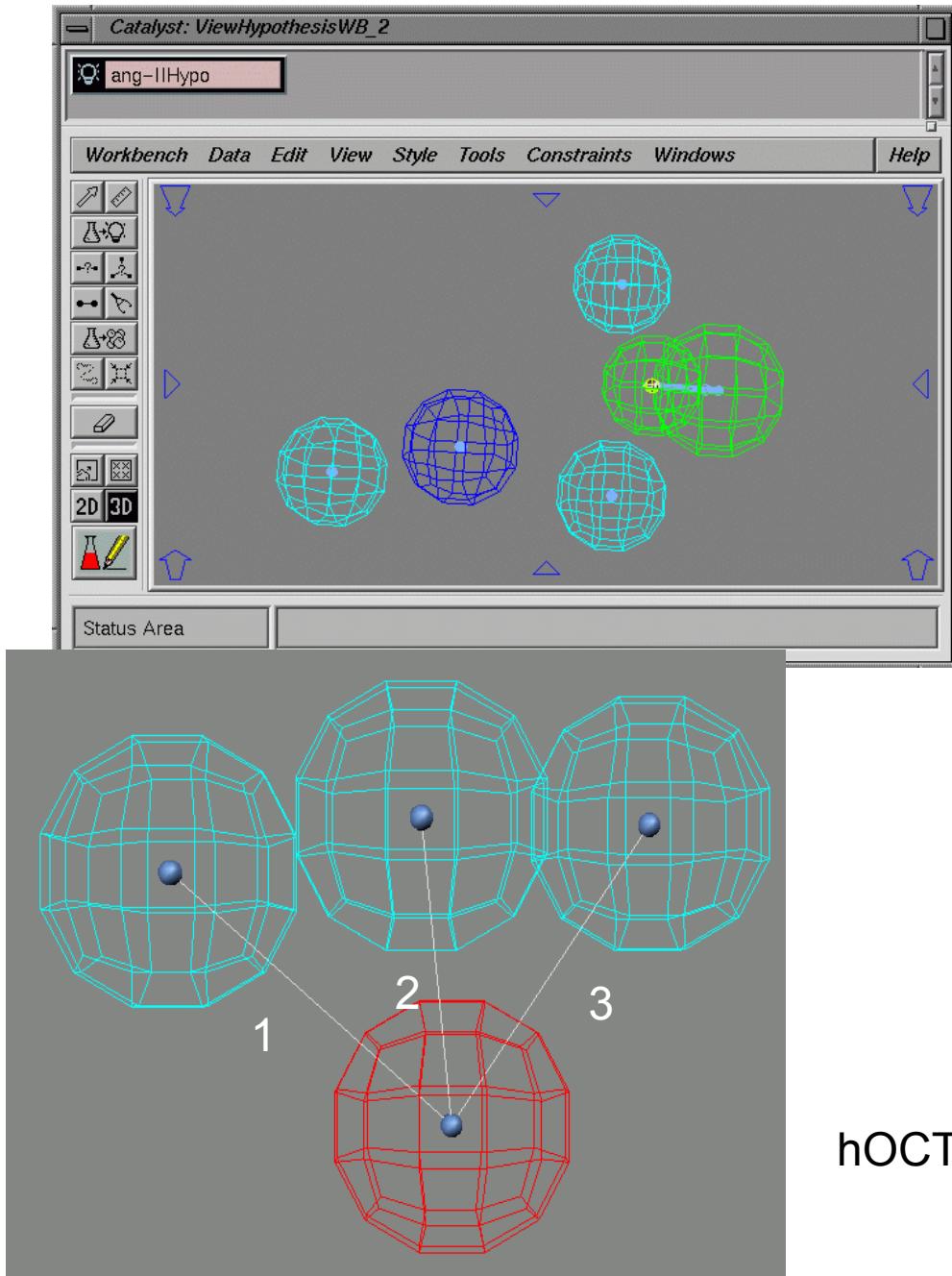
03/14/2007

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NCI -Frederick

Hits from the **Fast Flexible Search Database/Spreadsheet Search** on a sample database

Options to save the hits  
Fit the hits to the hypothesis

Figure shows Catalyst 4.9 interface from Accelrys Inc.



# 3D-Search

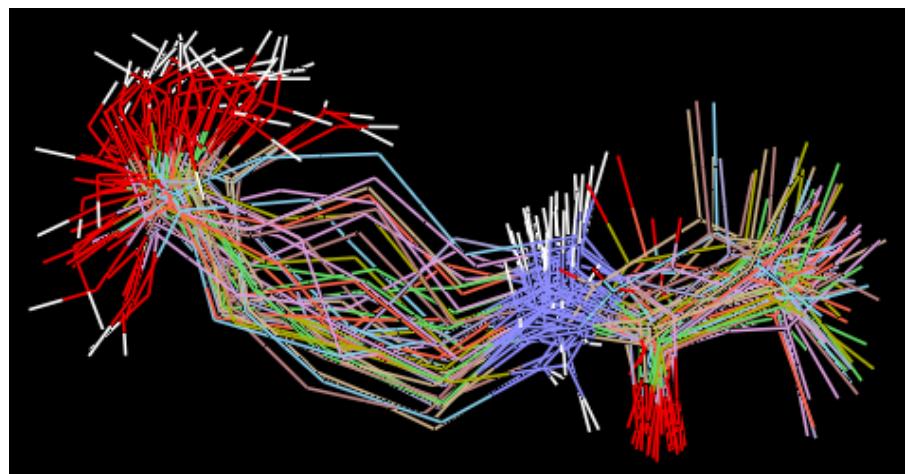
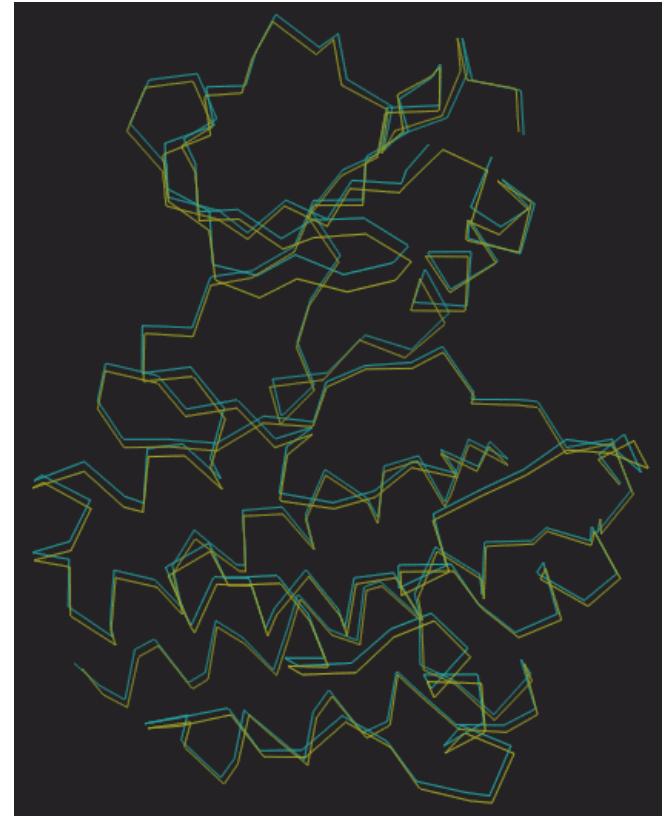
Cyan Hydrophobes Blue Neg Ionizable  
Green HB acceptor Red Positive Ion

# 3D-Structure Comparison

- Proteins
  - Homology Modeling, Evolutionary relationship, 3D-Folds
- Small Molecules
  - Only one conformation results in binding with the receptor. Identifying that active conformation is thus important.
  - Overlay can tell us how two molecules are similar

1QPC/  
1QPD

NMButy



# Molecular Dynamics (MD)

- Time dependent behavior of the molecular system
  - Local vibrations, conformational change of proteins and nucleic acids
- MD is based on classical Newton's motion
  - Equation of motion:  $F_i(t) = m_i a_i(t)$
  - Gradient of potential energy is used to calculate the forces
- Time-Step
  - $\Delta t$
- Several algorithms are available
  - Verlet, Velocity verlet etc.

Gromacs, Amber, Charmm, VMD, NEMD

# MD Overview

System

Interaction Potential

$$U_{ij} = 4\epsilon_{ij} [\sigma_{ij}/r_{ij}^{12} - \sigma_{ij}/r_{ij}^6]$$

Newton's Equation

$$d^2x_i/dt^2 = F_{xi}/m_i$$

Differential equations are solved using finite-difference methods

At time  $t$ : X, V and other dynamic information (known)

Predict at  $\Delta t$ , X, V, etc at reasonable accuracy

Time Step

$\Delta t$

$t_0$	$t_1$	$t_2$	$t_3$	$t_4$	$t_5$
-------	-------	-------	-------	-------	-------

Analysis: Correlation Functions etc.

# MD

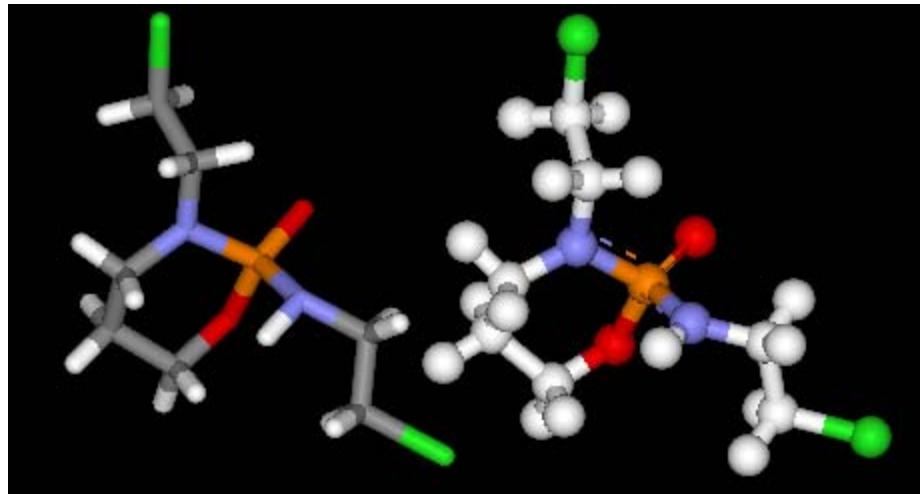
- A typical MD run consist of the following steps
  - Set Initial configuration/Velocity; Heating, Equilibration, Production, Saving configurations
- Applications: Dynamical Properties, MD can take information from NMR to perform a restrained MD.

# Quantum Mechanics (QM)

- Need for QM
  - MM and MD do not consider electrons explicitly (Born-Oppenheimer approximation)
    - When a drug molecule interact with a receptor. Primary interactions occur between the electron clouds. ELECTRONIC influence cannot be ignored always.
  - MM and MD cannot answer questions related to
    - Bond-forming or bond-breaking
    - Molecules not in ground state

# QM

- Basics:  $H\Psi = E\Psi$  Shrodinger's Equation E=Energy,  $\Psi$  = Wave Function.
  - Solve S.E to get the Energy and Wave Function, which inturn can be used to extract electronic properties (electron density etc.)
  - *ab-initio (from first principles)*, semi-empirical (approximations involved, for ex., only valence electrons are considered (AM1, PM3 etc.)
- QM can be used in conformational search and energy minimization
- Flavors: MOPAC, GAMESS etc.
- Applications: Minimization for small molecules, for conjugated systems, Descriptors for QSAR, Partial charges, transition state geometries & energies



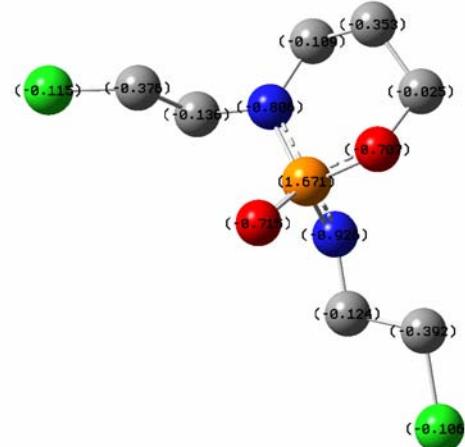
**R-Ifosfamide G03 Calculation  
RHF/6-31G(d) (before Min (L), After Min (R) )**

## Minimum input for QM calculation:

- Geometry (coordinates)
- Atomic number of each nucleus
- Overall charge, Spin State

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**QM**

```
%Nproc=8
%chk=M680410_RHF_6-31Gd.chk
%Mem=2200MB
#P RHF/6-31G(d) OPT
```

### M680410

0 1			
8	-1.61000	-8.06900	3.16800
6	-1.04900	-7.72000	2.02500
6	-0.78600	-8.67900	1.03000
6	-0.19200	-8.29900	-0.18100
1	0.00400	-9.04500	-0.93500
6	0.14700	-6.95300	-0.41700
.....			
.....			

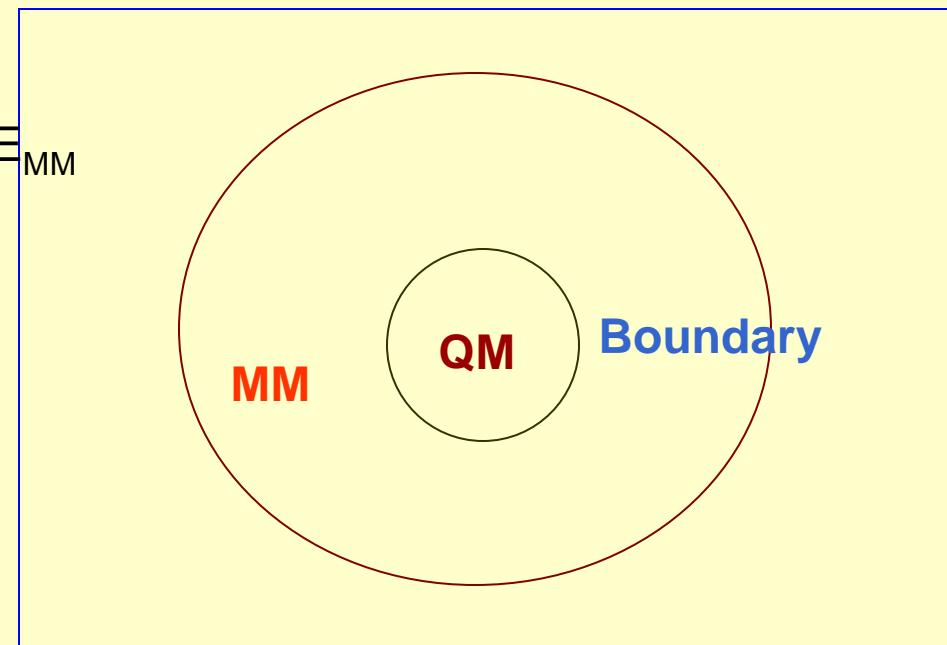
**Partial input Gaussian file (PBS)**

51

# Advanced Techniques: QM/MM

- MC (Monte-Carlo), Brownian Dynamics, QM/MM

$$E = E_{QM,elec} + E_{QM,vdW} + E_{MM}$$



*CHARMM has MM/QM module*

# Synonyms

## Semantics:

- Theoretical Chemistry: Quantum Mechanics
- Computational Chemistry: Quantum Mechanics and/or molecular mechanics and/or MM and/or Minimization and/or Conformational analysis and/or Any computational method used to understand the behavior of molecules
- Molecular Modelers use all the above methods

# Advances in Molecular Modeling/MD

Year	System	Total Time	Computer
------	--------	------------	----------

1983	DNA, Vacuum 12 and 24 bp (754/1530 atoms)	0.09 ns	Several weeks each on Vax780
2002	Channel Protein in lipid membrane (106,189 atoms,PME)	5.00 ns	30 hrs on a 500 proc. LeMieux terascale System  50 days, 23 proc Linux (Athlon)

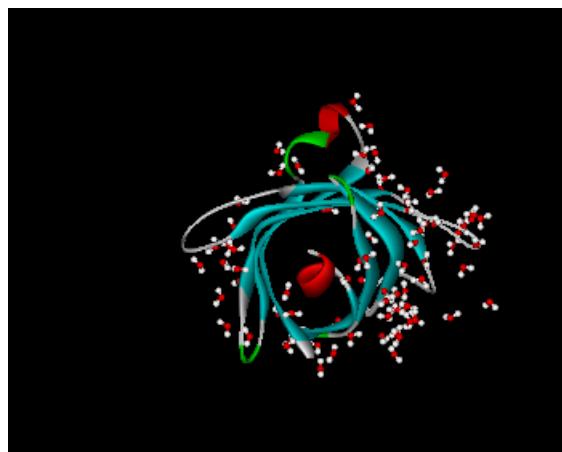
1 nanosecond =  $1 \times 10^{-9}$  seconds

*Molecular Modeling and Simulation  
Tamar Schlick*

# Applications of Molecular Modeling

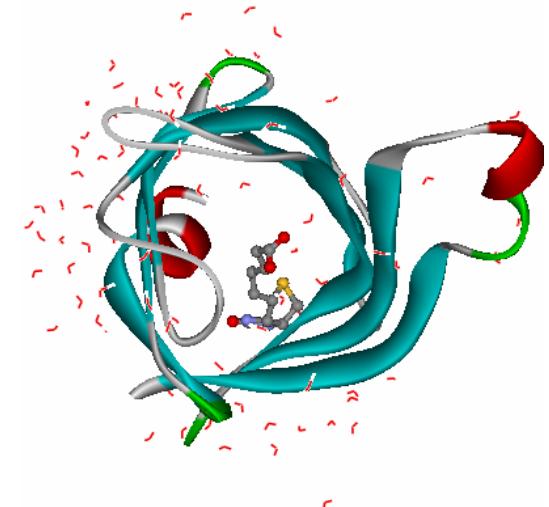
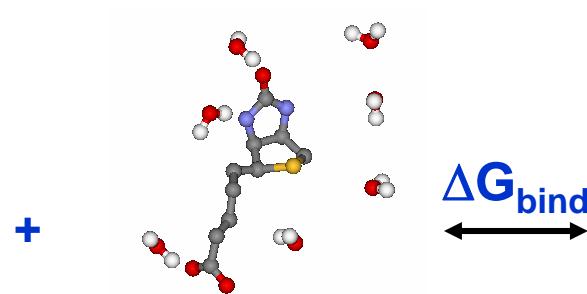
- Protein-Ligand Docking:
  - If you are interested in finding out how small molecules (drug molecule) interact and bind with a receptor of known 3-D structure
    - AutoDock, Dock, Flexi-dock etc.
- Protein-Protein Docking
  - Rigid body docking
    - 3D-Dock

Structure of  
Target  
molecule



# Docking

Conformational  
flexibility



$$\Delta G_{\text{bind}} = -RT \ln K_A$$

## Docking

- a) Structure modeling  
(Posing)
- b) Prediction of Activity

$$\text{Binding affinity} = K_A = K_i^{-1} = [E-I]/[E][I]$$

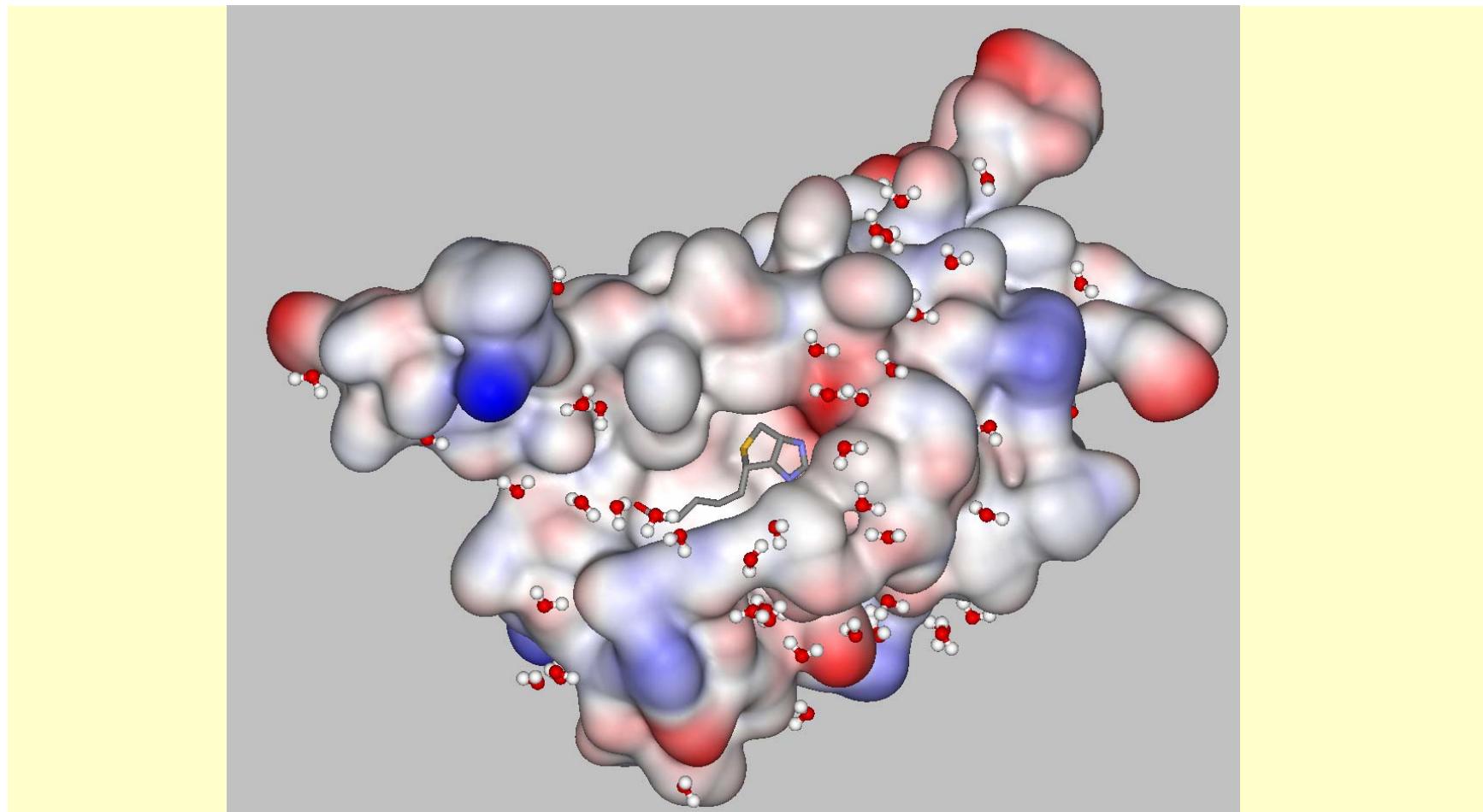
D. Kitchen et al, Nature Review, Vol 3, 935, 2004 (refs therein)

Kuntz et al several papers

Broojimans, N, Kuntz, I.D., Annu. Rev. Biophys. Biomol Str, 32, 335, 2003

Posing:  
Orientation and  
Conformation

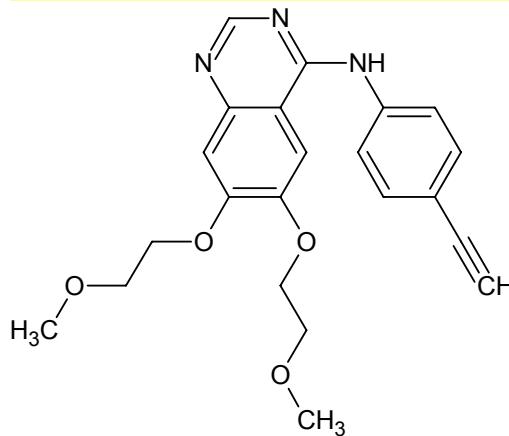
# Protein-Ligand Complex (1STP)



# Applications: Drug Design

A model must be wrong,  
in some respects,  
otherwise it would be the  
thing itself. The trick is to  
see where it is right

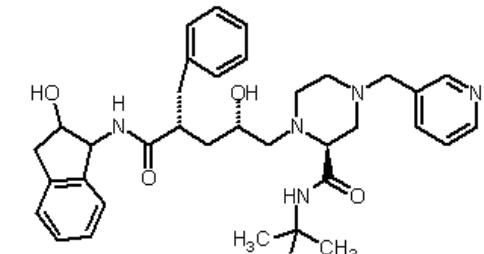
Henry A. Bent



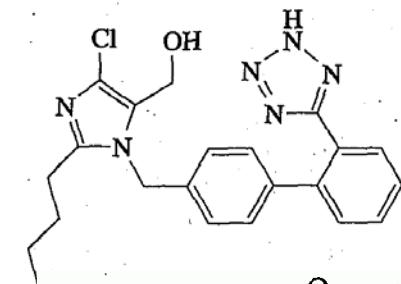
Erlotinib(Tarceva,OSI):  
Antineoplastic, 2004  
(Hormone-Sensitive Tumors)  
SBD

03/14/2007

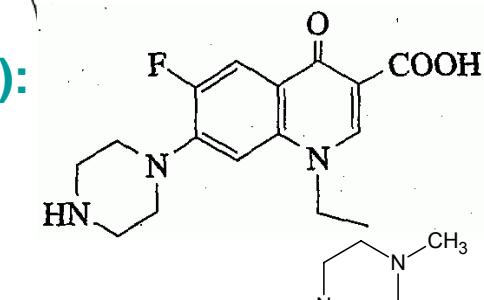
Indinavir (Crixivan, Merck)  
Antiviral, HIV, 1996  
MM/MM/Crystallography



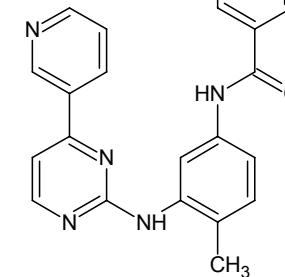
Losartan(Coozaar,Merck):  
Antihypertensive, 1994  
Structure Activity Study



Norfloxacin(Noroxin,Merck):  
Antibiotic, 1983  
QSAR



Imatinib (Gleevec,Novartis):  
Antineoplastic, 2001  
SBDD



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# Hands-on Exercise

- Instructions in the web-link
  - <http://nciiris.ncifcrf.gov/~ravichas/MM/MM.htm>

THANK YOU

# Selected Reference Books (Molecular Modeling)

- How Computational Chemistry Became Important in the Pharmaceutical Industry, D.B. Boyd, Reviews in Computational Chemistry, V23, 401 (2007)
- Molecular Modeling: Basic Principles and Applications, H.-D. Holtje, W. Sippl, D. Rognan and C. Folkers, second Edition, Wiley-VCH (2003)
- Molecular Modeling and Simulation, T. Schlick (2002)
- Molecular Modeling: Principles and Applications A.R. Leach (2001)
- Computer Simulation of liquids, M.P. Allen and D.J. Tildesley (1989)
- Discovering Genomics, Proteomics & Bioinformatics, A. M. Campbell and L. J. Heyer (2003)
- Bioinformatics: A practical Guide to the analysis of Genes and Proteins, Edited by A.D. Baxevanis and B.F.F. Quellette (2001)

# Selected Reference Books (Molecular Modeling)

- Developing Bioinformatics Computer Skills, C.Gibas and P. Jambeck (2001)
- Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins, Andreas D. Baxevanis, B.F. Oullette (2001)
- Introduction to Bioinformatics, Arthur M.Lesk (2002)
- Bioinformatics Basics, H. H. Rashidi and L.K. Buehler (2000)
- Introduction to Bioinformatics: Atwood and Parry-Smith (1999)
- *Chemoinformatics: A Textbook*, J. Gasteiger, T. Engel